

Origin of eukaryotic cells: was metabolic symbiosis based on hydrogen the driving force?

In a recent *TiBS* article, López-García and Moreira¹ discussed various hypotheses for the origin of eukaryotic cells. They concluded that the ancestral eukaryotic cell arose as a result of metabolic symbiosis (syntrophy) between a δ -proteobacterium, which generated hydrogen and CO₂ as waste products, and a methanogenic archaeobacterium, which depended on these products for its metabolism. Certain points made in this article are misleading and others need to be critically examined.

The authors focussed on two similar hypotheses proposed by them^{1,2} and Martin and Müller³. However, they did not give due credit to other authors for proposing a chimeric-symbiotic origin of the eukaryotic cell, which involved an archaeobacterium and a eubacterium⁴⁻¹¹. In an article published in *TiBS* (Ref. 10), we clearly indicated that this chimera resulted as a consequence of symbiotic association between these two groups of prokaryotes. This article also presented molecular evidence in support of the model on the basis of the observed duplication of genes for the molecular chaperone proteins Hsp70 and Hsp90, which took place at a very early stage (i.e. the formation of endoplasmic reticulum and nuclear envelope) in the formation of the eukaryotic cell^{10,12}. We referred to the process leading to the formation of the eukaryotic cell as 'primary fusion'^{4,13}, to emphasize the fact that the formation of the eukaryotic cell led to a complete integration of the genomes, as well as other characteristics of the two fusion partners¹⁴. The end result in this case was very different from other endosymbiotic events that led to the formation of mitochondria or plastids, which resulted in cells with host plus endosymbiont phenotypes^{4,13,14}. The primary fusion event that we proposed was not fundamentally different from the symbiotic event proposed by López-García and Moreira^{1,2} and by Martin and Müller³, except in its name.

The notion that the ancestral eukaryotic cell is a chimera with major gene contributions from both an archaeobacterium and a Gram-negative bacterium is now receiving increasing support^{5,8-10,15-19}. What is the nature of the driving or selective forces that led to the initial association and eventual

integration of these two widely different groups of prokaryotes to form a new kind of cell? López-García and Moreira^{1,2}, and Martin and Müller³ proposed that the driving force for this association between a methanogenic archaeobacterium and a proteobacterium is the metabolic symbiosis (or syntrophy) based on hydrogen. They favor this view on the basis of the widespread symbiotic association observed between these two groups of prokaryotes in nature²⁰. If this is the case, it is very difficult to envisage why this sort of symbiosis did not lead to the formation of eukaryotic-like cells on numerous independent occasions, and why in the biotopes, where such syntrophy is observed, eukaryotic cells at different intermediate stages of formation are not found. Their proposal is thus at variance with the strong and apparently incontrovertible evidence, based on different molecular sequences, that all extant eukaryotic species are derived from a common ancestor¹⁴, which indicates that the formation of the eukaryotic cell was a unique event that took place only once in the history of life.

There are several other observations that argue against the hydrogen hypothesis as the driving force.

(1) In all well-established cases of endosymbiotic association (viz. formation of mitochondria and plastids), the metabolic processes that formed the basis of the symbiotic association were retained in the resulting organisms^{4,13}. However, eukaryotic organisms have not retained any genes for methanogenesis that are proposed to be central to their origin.

(2) The proteobacterial division has now been indicated to have evolved much later than cyanobacteria^{14,21}, which indicates that the proposed symbiosis took place in a largely oxygenic atmosphere. The symbiotic association between an anaerobic, hydrogen-producing bacterium and a strictly anaerobic methanogenic archaeobacterium, which should produce an anaerobic organism, would be at a great selective disadvantage under oxygenic conditions.

(3) The proposal provides no rationale as to why various genes for the information transfer processes were retained from the archaeobacterial partner.

(4) Molecular sequence data indicate that among archaeobacteria, the eocyte group of archaeobacteria (i.e. thermoacidophilic) and not the methanogens are the closest relatives of eukaryotes^{14,22}.

Thus, the possibility that metabolic syntrophy based on hydrogen was the main driving force that led to the origin

of eukaryotic cells is counterindicated. An alternate proposal for the formation of the eukaryotic cell based on antibiotic selection pressure and oxygen-sensitivity has been proposed¹⁴, which can account for the uniqueness of the fusion event and the close similarity seen between archaeobacteria and eukaryotes in their information transfer processes.

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References

- López-García, P. and Moreira, D. (1999) *Trends Biochem. Sci.* 24, 88-93
- Moreira, D. and López-García, P. (1998) *J. Mol. Evol.* 47, 517-530
- Martin, W. and Müller, M. (1998) *Nature* 392, 37-41
- Margulis, L. (1970) *Origin of Eukaryotic Cells*, Yale University Press
- Zillig, W. (1991) *Curr. Opin. Genet. Dev.* 1, 544-551
- Gupta, R. S. and Golding, G. B. (1993) *J. Mol. Evol.* 37, 573-582
- Lake, J. A. and Rivera, M. C. (1994) *Proc. Natl. Acad. Sci. U. S. A.* 91, 2880-2881
- Sogin, M. L. (1991) *Curr. Opin. Genet. Dev.* 1, 457-463
- Margulis, L. (1996) *Proc. Natl. Acad. Sci. U. S. A.* 93, 1071-1076
- Gupta, R. S. and Golding, G. B. (1996) *Trends Biochem. Sci.* 21, 166-171
- Karlin, S., Mrazek, J. and Campbell, A. M. (1997) *J. Bacteriol.* 179, 3899-3913
- Gupta, R. S., Aitken, K., Falah, M. and Singh, B. (1994) *Proc. Natl. Acad. Sci. U. S. A.* 91, 2895-2899
- Gray, M. W. (1992) *Int. Rev. Cytol.* 141, 233-357
- Gupta, R. S. (1998) *Microbiol. Mol. Biol. Rev.* 62, 1435-1491
- Golding, G. B. and Gupta, R. S. (1995) *Mol. Biol. Evol.* 12, 1-6
- Feng, D. F., Cho, G. and Doolittle, R. F. (1997) *Proc. Natl. Acad. Sci. U. S. A.* 94, 13028-13033
- Ribeiro, S. and Golding, G. B. (1998) *Mol. Biol. Evol.* 15, 779-788
- Rivera, M., Jain, R., Moore, J. E. and Lake, J. A. (1999) *Proc. Natl. Acad. Sci. U. S. A.* 95, 6239-6244
- Doolittle, W. F. (1998) *Nature* 392, 15-16
- Fenchel, T. and Finlay, B. J. (1995) in *Ecology and Evolution in Anoxic World* (May, R. M. and Harvery, P. H., eds), pp. 85-98, Oxford University Press
- Gupta, R. S., Mukhtar, T. and Singh, B. (1999) *Mol. Microbiol.* 32, 893-906
- Rivera, M. C. and Lake, J. A. (1992) *Science* 257, 74-76

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